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Efficacy of Jawarish Shahi a herbal formulation in irritable bowel syndrome: An open-labeled single-arm clinical trial

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ABSTRACT

Background and aim: Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders characterized by chronic recurrent abdominal pain related to a change in bowel habit or defecation frequency and commonly accompanied by anxiety and depression affecting about 10% population globally. Jawarish Shahi (JS) is a special dosage form prepared for gastrointestinal disorders in Unani medicine containing *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Coriandrum sativum* L., *Elettaria cardamomum* (L.) Maton and *Salix caprea* L. Considering the antioxidant, immunomodulatory, anti-spasmodic analgesic, antidiarrheal, antisecretory, laxative, anti-inflammatory, anxiolytic, and antidepressant properties, the present study was aimed to evaluate the efficacy of JS in IBS.

Experimental procedure: This single-arm open-labeled clinical trial was conducted on 26 male and female patients of IBS according to Rome IV criteria, aged 18–50 years with moderate symptoms. JS was given 7 g orally twice a day after meal with water for 45 days. IBS Severity Scoring Scale (IBS-SSS) was used for efficacy outcomes and the difference was analyzed from baseline to the subsequent follow-ups.

Results: Data analysis of subsequent followup showed a significant decrease in IBS-SSS scores except for 2nd followup, scores decreased from 229.50 ± 75.91 to 203.12 ± 71.71 ($p < 0.1018$), 150.61 ± 55.32 ($p < 0.0001$), and 123.76 ± 54.81 ($p < 0.0001$) at 0, 15th, 30th, 45th day of follow up respectively.

Conclusion: The present study revealed that JS is safe and effective in reducing the overall symptoms of IBS in respect to its severity and impact on quality of life and can be used as an alternate as well as a complementary treatment in IBS.

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1. Introduction

Irritable bowel syndrome (IBS) is a chronic, relapsing, and sometimes disabling disorder of gut-brain interactions, characterized by abdominal pain or discomfort and accompanied by altered bowel habits (constipation, diarrhea, or alternating constipation and diarrhea) often coupled with abdominal bloating in the absence of detectable structural pathology.^{1–4} IBS has a strong impact on health-related quality of life, with its consequences in

reduced work productivity, increased absenteeism, and elevated health care use and costs.⁵ IBS has been estimated to be the cause of between 8.5 and 21.6 days off work per year, while the chronicity of IBS symptoms leads to increased use of secondary health care services with health care costs of up to 4.1 billion Euros per year in Germany.⁶ It affects roughly about 10%–20% (Globally) of the general population with a female predominance and the majority of patients being diagnosed in primary care. The highest occurrence was recorded in South America at 21% and the lowest rate reported in South Asia at 7%.^{7–10} In Asia, the reported prevalence is in the range of 1–10%. While in India, the prevalence of IBS ranges from 4.2 to 7.5% with a high prevalence among men.^{11,12}

The etiopathogenesis of IBS is not fully understood, nevertheless, many factors have been suggested to be involved in the pathogenesis of IBS, such as brain-gut-axis defects, abnormal gut flora, visceral hypersensitivity, dysfunctions in colonic motility, a

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List of abbreviations

| | |
|---------|--------------------------------------|
| CRF | Case record form |
| IBS | Irritable bowel syndrome |
| IBS-SSS | IBS severity scoring scale |
| GI | Gastrointestinal |
| NIUM | National institute of Unani medicine |
| DM | Diabetes mellitus |
| CRP | C-reactive protein |
| IBD | Inflammatory bowel disease |
| KFT | Kidney function test |
| LFT | Liver function test |
| ESR | Erythrocyte sedimentation rate) |
| JS | Jawarish Shahi |

| | |
|---------|--|
| IEC | Institutional ethical committee |
| ICH-GCP | International Committee on Harmonization of Good Clinical Practice |
| CTRI | Clinical Trial Registry of India |
| CONSORT | Consolidated standards of reporting trials |
| ITT | Intention to treat |
| LOCF | Last observation carried forward |
| CNS | central nervous system |
| 5-HT | 5-hydroxytryptamine |
| BDNF | Brain-derived neurotrophic factor |
| CREB | cAMP response element-binding protein |
| GABAA | γ -Aminobutyric acid type A |
| cAMP | Cyclic adenosine monophosphate |

disorder in serotonin secretion, bile acid malabsorption, psychological disorders, genetic, altered immune response and environmental factors depending on the individual.¹³ Based on Rome-IV criteria, IBS is categorized according to the predominant disorder in bowel habits into four subtypes as diarrhea predominant (IBS-D), constipated predominant (IBS-C), mixed symptoms of diarrhea and constipation (IBS-M), and last one an unclassified (IBS-U).¹⁴

The management of IBS is challenging due to the complex nature and uncertain pathophysiology of the disease.⁷ Although the conventional modalities of treatments produce favorable outcomes but still there have been reported side effects.¹⁵ Loperamide has been found to be efficacious for multiple symptoms of IBS in persons with all types of IBS. however, common adverse effects of loperamide observed in the general population included nausea, cramping, and constipation,¹⁶ while antispasmodic like dicyclomine cause drowsiness, dry mouth, blurred vision, inability to urinate in long term use. Antispasmodics are relatively safe, but one should be aware of the potential anticholinergic side effects and contraindications. The anticholinergic side effects include constipation, dry mouth, visual disturbances, and urinary retention in long term use.^{16,17}

In Unani medicine various renowned physicians and philosophers have described gastrointestinal disorders and discussed in detail in their treatise, they have described diseased conditions like “Zalaq-ul-Am'aa, Is'hal dimagi, Zaheer kazib and Qabz which are similar to the symptoms of IBS.¹⁸ Various single as well as compound herbal pharmacopeial formulations are mentioned and have been prescribed which are still in use in different regions by the physicians of Unani medicine for the management of these disease conditions.^{18,19} Jawarish Shahi (JS) is one of the polyherbal formulations specially prepared for gastrointestinal disorders and IBS-like conditions in Unani Medicine. The Arabic term *Jawarish* is derived from the Persian word “Gowarish” which means digestion. It is a semisolid traditional pharmaceutical dosage form in which ingredients are powdered in coarse particle size to ensure a longer stay in the stomach and serve as a slow gastric tonic and digestive medication. Based on the ingredients *Jawarish* has various gastrointestinal therapeutic effects such as stomach tonic, digestive, carminative, laxative, astringent, visceral analgesic, anti-hemorrhoid, antiemetic, emetic, anti-reflux, and anti-colic, moreover, some of them possess cardiac, brain liver tonic, aphrodisiac and analgesic effects. JS contains the following ingredients (as shown in Table 1.) such as *Murabba Halela*, (*Terminalia chebula* Retz.) *Murabba Amla*, (*Phyllanthus emblica* L.), *Heel Khurd* (*Elettaria cardamomum* (L.) Maton), *Kishneez* (*Coriandrum sativum* L.), *Arqe Bedmushk* (*Salix caprea* L.), which possess major properties of *Muqawwimeda* (stomachic), *Muqawwi ama* (intestinal tonic) *Kasir-*

e-riyah (carminative), *Muhallil* (resolvent), *Musakkin-e-alam* (analgesic), and *Qabiz* (astringent).^{19,20}

The herbs like *Phyllanthus emblica* L. and *Coriandrum sativum* L. of JS have been researched widely for their phytochemical and pharmacological properties in different biomedical studies. The biomedical studies and diverse clinical use of different herbs of JS validate the traditional use of JS in different gastrointestinal disorders. *Elettaria cardamomum* (L.) Maton and *Phyllanthus emblica* L. have been widely researched and reported to have gastro-protective activity.^{21,22} *Phyllanthus emblica* L. reported to have antioxidant, immunomodulatory, analgesic, cytoprotective, anti-tussive, antidiarrheal, antisecretory, and spasmolytic activities.^{22,23} *Coriandrum sativum* is reported to have anti-inflammatory and anti-colitis activities when on acetic acid-induced colitis in rats was demonstrated in an experimental model of acute colitis.²⁴ *Elettaria cardamomum* (L.) Maton and *Coriandrum sativum* L. possess analgesic and antispasmodic activity, antioxidant activity.^{25,26} *Terminalia chebula* Retz. Fructus possesses significant antidiarrhoeal activity due to inhibiting the gastrointestinal propulsion and fluid secretion.²⁷ *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Elettaria cardamomum* (L.) Maton, *Coriandrum sativum* L. and *Salix caprea* L. are also reported to possess anxiolytic activity, antidepressant activity, sedative-hypnotic activity, and antioxidant activity.^{27–31} Therefore given the above facts and considering the phytochemical and biomedical reports the present study was aimed to evaluate the efficacy of JS in irritable bowel syndrome on modern scientific parameters.

2. Material and methods

2.1. Study design and setting

The current study was a single-arm open labeled with pre and post-analysis clinical trial design. The trial was carried out in the Hospital of the National Institute of Unani Medicine, Bengaluru from Oct 2020 to March 2021.

2.2. Ethical considerations

The study protocol was in compliance with the Declaration of Helsinki and standards provided by the International Committee on Harmonization of Good Clinical Practice (ICH-GCP) guidelines. Before the commencement of the trial, the study protocol was submitted to the institutional ethical committee (IEC number; NIUM/IEC/2018-19/002/Moal/02 Dated: 21-03-2019) of NIUM, Bengaluru, and approved. The trial was registered prospectively by the Clinical Trial Registry under clinical trial registration number-

Table-1

The composition of Jawarish Shahi was used in this trial.

| Unani Name | Botanical name | Family | Part used | Weight |
|----------------|--|---------------|------------|--------|
| Murabba Amla | <i>Phyllanthus emblica</i> L. | Euphorbiaceae | Fruit | 4 nos. |
| Murabba Halela | <i>Terminalia chebula</i> Retz. | Combretaceae | Fruit | 5 nos. |
| Kishneez | <i>Coriandrum sativum</i> L. | Umbelliferae | Fruit/Seed | 12 gms |
| Heel Khurd | <i>Elettaria cardamomum</i> (L.) Maton | Zingiberaceae | Fruit/Seed | 03 gms |
| Arq Bedmushk | <i>Salix caprea</i> L. | Salicaceae | Leaves | Q.S. |

CTRI/2020/03/023790. All the participants were explained about the study and provided verbal and written informed consent forms, after getting their signed written informed consent they were enrolled in the study.

2.3. Sample size

With a probability of 95%, error rate of 5% ($\alpha = 0.05$) and power of 80%, the sample size estimated as, $N = (Z\alpha)^2 s^2 / d^2$, [where $Z\alpha$ = normal deviate for one tailed hypothesis, s = standard deviation, d = difference of means]³² which gives a sample of 24 subjects, if the allowance of 10% for missing, losses to follow-up, withdrawals is assumed, then the corrected sample came as 26. Mean and standard deviation obtained from the previous study.³³

2.4. Inclusion criteria

Clinically diagnosed patients of IBS according to the Rome-IV criteria were included.³⁴

Patients of either sex in the age group of 18–50 years. Patients who have agreed to sign the written informed consent and follow the protocol.

2.5. Exclusion criteria

1. Patients suffering from systemic illnesses like Hypertension, Diabetes Mellitus, Malignancy, Liver or Kidney dysfunction. 2. Patients suffering from IBD (Ulcerative colitis, Crohn's disease), Amoebic dysentery, Intestinal tuberculosis, or Intestinal obstruction. 3. Patients below 18 and above 50 years. 4. Pregnant and lactating women. 5. Patients with laboratory abnormalities with hemoglobin <9 g/dl, AST & ALT >120 IU/L, serum creatinine >1.5 mg/dl, occult blood in stool, and increased CRP were among the exclusion criteria.

2.5.1. Herbal drug (Jawarish-Shahi) preparation and administration

JS is prepared as per the good manufacturing practice guidelines of the Pharmacopeia of Unani Medicine. The stepwise method is as follows: First, *Murabba Amla* and *Murabba halela* is prepared separately. *Murabba*, or Preserver: a special preparation of fruits preserved in sugar/honey to make available in odd season and remains beneficial after a long time also. The taste of fruit may be improved from this process also. Fresh fruits of *Amla* (*Phyllanthus emblica* L.) and *Halela* (*Terminalia chebula* Retz. fruit) are boiled separately in water till these become soft, fruits are taken out of the water and dried. A *Qiwam* (basic solution of particular consistency) of sugar solution is prepared and fruits are kept in solution. On the second day the *Qiwam* is boiled up to a desired consistency of solution to become *Jawarish*. After that *Murabba Amla* and *Murabba halela* *Kishneez* (*Coriandrum sativum* L.), *Elaichi Khurd*, (*Elettaria cardamomum* (L.) Maton) are mashed and ground in *Arq- Bed Mushk* (*Salix caprea* L. distillate) in the required quantity, after that the preparation is kept in a pot and water and white sugar are added in it and finally heated on a flame to make a *Qiwam* of *Jawarish*. The preparation is ready to serve and stored in an airtight

container.^{19,20}

In this study we used the test drug *Jawarish-Shahi* (JS) manufactured by Hamdard Laboratories (Unani pharmaceutical company) New Delhi, India, that was purchased from a retail outlet in Bengaluru. The patients were given “JS” as a test drug in a fixed dose of 7 g orally twice a day after meal with water for 45 days.^{19,20} The patients were not allowed to take any other concomitant medication/treatment that might influence the research throughout the study.

2.6. Study outcome measure; IBS Severity Scoring Scale (IBS-SSS)

The IBS-SSS is a 5-question survey that asks the severity of abdominal pain, frequency of abdominal pain, severity of abdominal distention, dissatisfaction with bowel habits, and interference with quality of life over the past 10 days. Subjects respond to each question on a 100-point visual analog scale. Scores on the IBS-SSS can range from 0 to 500 with higher scores indicating more severe symptoms. Subjects can be categorized as having mild (75–175), moderate (175–300), or severe (>300) IBS. A decrease of 50 points is associated with a clinically meaningful improvement.^{35,36} A European study found that greater symptom severity in IBS outpatients, when measured by the IBS-SSS, was associated with poorer Quality of life and IBS-SSS could be used for selecting symptomatic patients for clinical trials and for measuring response to treatment.³⁷

2.7. Safety assessment: safety, tolerability and adverse event monitoring

All the patients were followed and clinically assessed weekly and were closely monitored for any suspicious events during the treatment phases of the trial. The participants were encouraged to report any symptoms and discomfort, even unusual ones. After giving proper information and explanation about investigations blood tests were taken for complete blood count, aspartate aminotransferase, alanine aminotransferase, blood urea, and creatinine and checked at baseline and after the trial was completed.

2.8. Study duration and follow-up

All the patients were enrolled in the study were asked to visit NIUM Hospital OPD for proper follow-up at every 15th day (0, 15th, 30th, 45th day) and they were clinically assessed at every visit during the study. IBS-SSS scores were recorded at each visit and laboratory investigations were done at baseline and after treatment. Failure to follow protocol therapy, non-compliance and adverse reaction to the intervention was considered to be withdrawn criteria.

2.9. Statistical methods for analysis

The Statistical software, namely SPSS 25.0, and R environment ver.3.2.2 and were used for the analysis of the data and Microsoft

Word and Excel have been used to generate graphs, tables, mean, etc. Results on continuous measurements are presented on Mean \pm SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at a 5% level of significance. Paired proportion test has been used to find the significance of proportion in paired data. A smaller percentage of improvement becomes significant at the lower tail compared to the higher tail.

3. Results

3.1. Patients at baseline

The baseline characteristic of the patients is mentioned in Table 2. Out of 26 patients, there were 3 females and 23 males with a mean age of 32.26 ± 7.06 years with moderate disease severity. 26 patients were included in the study, Fig. 1 shows the disposition and the flow of the patients through the study. 22 (85%) patients completed the study, and 4 (15%) patients were lost to follow-up. Statistical analysis was done on an intention to treat (ITT) basis using the last observation carried forward method (LOCF).

3.2. Efficacy outcomes

Significant changes were observed in efficacy outcomes when analyzed from baseline, subsequent follow-up and at end of the treatment. The disease severity scores as evaluated by the IBS-SSS at subsequent visits are summarized in Table 3. The observed mean \pm SD score of IBS-SSS decreased from 229.50 ± 75.91 to 203.12 ± 71.71 ($p < 0.1018$), 150.61 ± 55.32 ($p < 0.0001$), and 123.76 ± 54.81 ($p < 0.0001$), at 0, 15th, 30th, 45th day, which was found moderately significant at first follow up, whereas, at second and third followup, it was highly significant.

3.3. Safety evaluation

The patients were well-followed-up and clinically assessed during the study period, no adverse events were reported and the drug was well tolerated. No anaphylactic episodes or other major imbalances in any system organ affected by adverse events were reported during the study period. The evaluations of markers of liver and kidney functions (Table 4.) were all within the normal range when analyzed from baseline and end of the study.

4. Discussion

The results of the present study demonstrated that the JS

treatment significantly reduced IBS-SSS scores ($p < 0.0001$) from moderate at baseline (229.50 ± 75.91) to mild (123.76 ± 54.81) on 45th day. The decreasing trend in IBS-SSS scores implied that the symptoms of IBS, including pain, distention, bowel habit and interfering with patient life in general (Negative impact on the quality of life) could be controlled by the JS treatment. The beneficial pharmacological actions of JS and its ingredients such as Muqawwi meda (stomachic), Muhallil (resolvent), Musakkin-e-alam (Analgesic) helps to reduce the severity of pain and regulate the bowel movements.¹⁹

Recent evidences suggest that a subset of IBS patients demonstrated altered mucosal immune function and low-grade inflammation. One potential mechanism behind the observed effect could be the anti-inflammatory and gastric mucosal protective effect of *Elettaria cardamomum* (L.) Maton, and *Coriandrum sativum* Linn.^{25,26} The gastroprotective effect of these ingredients might be related to the free-radical scavenging property of different antioxidant constituents such as linalool, flavonoids, coumarins, catechins, terpenes, and polyphenolic compounds.²⁶ While relieving in bloating/abdominal distention might be the result of Kasir-eriyah (carminative) and Muhallil (resolvent) properties of ingredients of Jawarish shahi.¹⁹ The mechanism of relieving in bloating/abdominal distention might be due to analgesic & antispasmodic, antioxidant activity of *Elettaria cardamomum* (L.) Maton, and *Coriandrum sativum* Linn.^{25,26} Cardamom oil was found to exhibit its inhibitory effect against the contractile response elicited by the neurotransmitter acetylcholine on rabbit intestine preparation. Acetylcholine (ACh) is the most common neurotransmitter at the parasympathetic nerve ending to induce smooth muscle contractions, cardamom oil as an antispasmodic inhibits intestinal smooth muscle depolarization at the muscarinic receptor. This suggests that cardamom exerts its effect by muscarinic receptor blockade.²⁵

The other symptoms related to altered stool frequency and altered stool consistency showed a remarkable improvement and the plausible mechanism of such effect could be attributed to Qabiz (astringent) and Muqawwi meda (stomachic) wa Muqawwi A'ma (intestinal tonic), properties of the ingredients. These activities help to regulate bowel function, reduces the frequency of stool, and severity of constipation and diarrhea.¹⁹ GI motility regulation and antidiarrheal, antisecretory, and spasmolytic activities are reported by *Phyllanthus emblica* L. and *Terminalia chebula* Retz. of Jawarish Shahi. Studies demonstrated that the presence of phenolic compounds, alkaloids, flavonoids, terpenes, and tannins might be responsible for the antidiarrheal, antisecretory, and spasmolytic activity of *Phyllanthus emblica* L., which has been reported in various studies.²³ Another study reported that the methanol extract of *Phyllanthus emblica* L., possesses significant antidiarrheal activity

Table-2
Baseline characteristic details of patients.

| Age in years (mean + SD) | | 32.26 + 7.06 | |
|--------------------------|------------------------|--------------|--------|
| Gender | Female/Male | 03/23 | 12/88% |
| Religion | Hindu/Muslim | 06/20 | 24/76% |
| Marital Status | Married/Unmarried | 20/6 | 76/24% |
| Diet | Mixed diet/Vegetarians | 24/2 | 92/8% |
| Lifestyle Status | Moderate | 17 | 65.38% |
| | Sedentary | 2 | 7.69% |
| | Strenuous | 7 | 26.93% |
| | Tea | 11 | 42.30% |
| Addiction | Smoking | 11 | 15.40% |
| | Alcohol | 4 | 42.30% |
| | | 16 | 61.53% |
| Region | Urban | 10 | 38.47% |
| | Rural | 15 | 57.69% |
| Psychological disorders | Anxiety | 6 | 23.07% |
| | Depression | | |

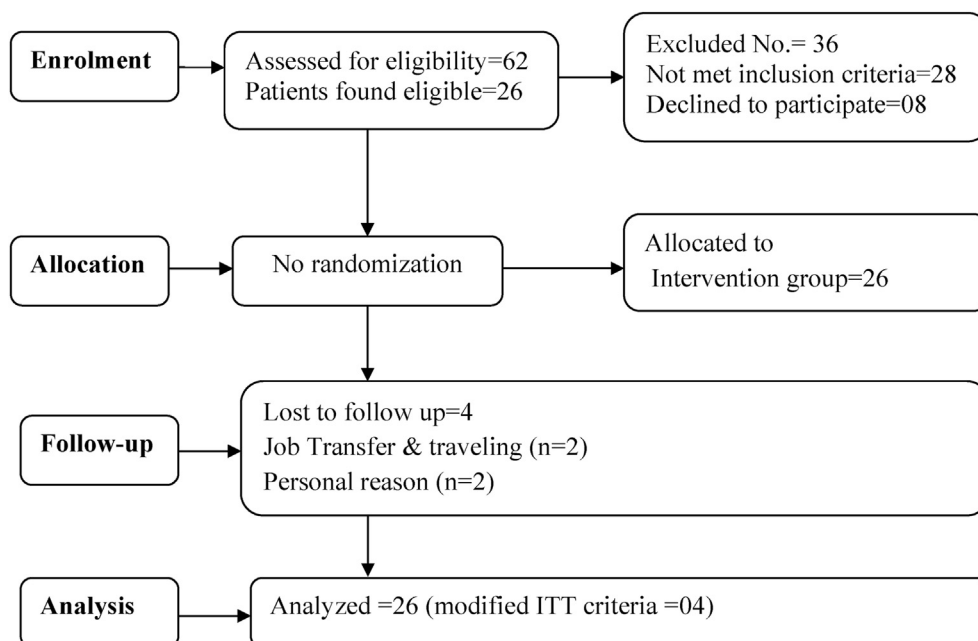


Fig. 1. CONSORT Flow chart of patients studied.

Table-3

The outcome measure IBS-SSS score (Mean \pm SD) at subsequent followup.

| Follow-up | BT (0day) | 15th Day | 30th Day | AT (45th day) | P-value |
|------------|--------------------|--------------------|--------------------|--------------------|----------|
| IBS-SSS | 229.50 \pm 75.91 | 203.12 \pm 71.71 | 150.61 \pm 55.32 | 123.76 \pm 54.81 | 0.0001** |
| Difference | — | –26.38 | –78.88 | –105.73 | |
| P-value | — | 0.1018 | 0.0001** | 0.0001** | |

**Highly significant change was noted ($p < 0.0001$) using Student *t*-test (Paired).

BT, before treatment; AT, after treatment.

Table-4

Means and standard deviation of the safety measures.

| Investigations | BT | AT | P-value |
|----------------|-------------------|-------|---------|
| AST | 31.61 \pm 14.12 | 29.03 | 0.17 |
| ALT | 32.50 \pm 11.92 | 33.46 | 0.33 |
| B. Urea | 25.15 \pm 6.88 | 27.73 | 0.06 |
| S. Creatinine | 1.0 \pm 0.13 | 1.01 | 0.33 |

BT, before treatment; AT, after treatment; BU, blood urea; SC, serum creatinine; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

due to its inhibitory effect on both gastrointestinal propulsion and fluid secretion.³⁸ *Terminalia chebula* Retz. which is a chief ingredient of JS possesses antidiarrheal and antidyseutery activity.³⁹ An in vivo study demonstrated that phytochemical analysis revealed that *Terminalia chebula* Retz. fructus possesses significant antidiarrheal activity due to inhibiting gastrointestinal propulsion and fluid secretion. The ethyl acetate fraction is the most active fraction that decreases the frequency of stooling. The major components mainly include hydrolyzable tannins, including gallic acid, 3,4,6-triOgalloyl-b-D-Glc, corilagin, and ellagic acid. These constituents may mediate the antidiarrheal property.⁴⁰ Bowel regulation and relief in constipation symptoms may be attributed to the *Terminalia chebula* Retz. which acts as a Mulayyin (laxative) and Mushil Khafeef (mild purgative) in Unani medicine which is validated in an animal study that *Terminalia chebula* Retz. possesses laxative and gastroprotective activity.^{40,41}

Studies suggest that psychological and psychiatric comorbidity is often reported among IBS patients. These psychosocial factors

influence the illness experience, patient expectations, and treatment outcome of IBS patients. Multiple studies have indicated positive correlations among psychological distress, daily stress, and GI symptom aggravation that triggered IBS symptoms.¹⁴ We assessed the anxiety and depression disorders in our study as shown in Table. 2, we found 15 out of 26 patient suffering from some sort of anxiety and 6 out of 26 patient suffering with depression at baseline. Higher prevalence of IBS associates with psychological factors such as stress and anxiety.⁹ The herbs in JS like *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Elettaria cardamomum* (L.) Maton, *Coriandrum sativum* L. and *Salix caprea* L. are also reported to possess anxiolytic activity, antidepressant activity, sedative-hypnotic activity, and antioxidant activity.^{27–31} In our study improvement in the IBS-SS may be associated with the certain effect on the psychological disorders like anxiety and depression and the plausible mechanism of such effect could be attributed to these pharmacological effects of JS. An animal study demonstrated that high flavonoids contents of *Elettaria cardamomum* (L.) Maton especially quercetin possesses anti-depressant and anxiolytic effect.³⁰ The Extracts of *Coriandrum sativum* L. might produce an antidepressant-like effect by interacting with α 1 adrenoceptor dopamine D2 receptor and GABAergic receptor, through increasing level norepinephrine and dopamine and decreasing level of Dopamine.⁴² *Phyllanthus emblica* L. contains flavonoids, saponins, and tannins that possess activity against many CNS disorders like depression and anxiety.²⁸ Chebulinic acid is an ellagitannin that was isolated from hydroalcoholic extraction of *Terminalia chebula* Retz. reported to possess antidepressant and

anxiolytic properties. The effect of *Terminalia chebula* Retz. was assessed on various neurotransmitters and mRNA and protein expression in a mouse model. The extract of *Terminalia chebula* Retz. significantly reduced the serum cortisol levels and elevated the monoamine neurotransmitters such as 5- hydroxytryptamine (5-HT), dopamine and norepinephrine levels in brain tissues. Another gene expressions study revealed that the brain-derived neurotrophic factor (BDNF), cAMP response element-binding protein (CREB), GABAA and 5-HT1A were up-regulated by a tannin-rich extract from *Terminalia chebula* Retz.. Additionally, the treatment of the same extract showed significant anxiolytic activity against the picrotoxin-induced anxiety model.²⁷ The Anxiolytic activity of *Coriandrum sativum* L. is likely to be associated with its essential oil content and flavonoids. It is reported that coriander seed oil contains linalool (60–70%) as the major essential oil component. Linalool has marked anxiolytic and sedative effects are also shown in human subjects.²⁹

Gut microbiota is known to fulfil human host's metabolism, physiology, and health homeostasis functions. Change in gut microbial community composition (so-called dysbiosis) have been found to be correlated with various disorders, ranging from cardiometabolic diseases and cancer. Among FGID, irritable bowel syndrome is most likely associated with gut microbial community composition changes.⁴³ Herbal medicines that are administered orally enter the body and interact with the gut microbiota (GM) in the intestine. Studies have found that after the administration of herbal medicines the composition of the GM can change, and improve certain disease conditions such as Diabetes Mellitus. There are two main pathways are described by which herbal medicines have physiological functions after interacting with the GM. One pathway is that the GM “digests” the herbal medicines into absorbable active small molecules, which then enter the body and induce physiological changes. The other pathway is that herbal medicines change the GM and its secretions, which inducing physiological changes.⁴⁴ *Phyllanthus emblica* L. inhibits the growth of pathogenic microorganisms in the intestines which may aggravate intestinal symptoms. Polyphenols in *Phyllanthus emblica* L. and *Terminalia chebula* Retz can modulate the human gut microbiota by promoting the growth of beneficial Bifidobacterium and Lactobacillus species and inhibiting the growth of undesirable intestinal resident pathogen, which may induce the inflammatory reaction. Moreover, polyphenols e.g. chebulinic or ellagic acids, can be transformed by the human intestinal microbiota into various active metabolites, including urolithins, which modulate the inflammatory process by generating anti-inflammatory compounds and preventing oxidative injuries of enterocytes.⁴⁵ Tannins present in *Phyllanthus emblica* L. is intensively metabolized by certain gut bacteria, leading to the generation of small, bioavailable and potentially bioactive metabolites. Moreover, interaction with these compounds may exert a prebiotic-like effect on gut microbiota.⁴³ The role of possible manipulation of gut microbiota by JS may represent a new therapeutic strategy and become an effective way of restoring gut microbiome in patients with impaired lower GI function e.g. patients with FGID like IBS.⁴⁵

The last question of IBS SSS questionnaire (outcome measure) seeks to combine global well-being and an overall view on quality of life (a single global quality of life question) as it relates especially to irritable bowel syndrome. The quality of life improvement as a result of overall improvement in IBS symptom severity such as recurrent abdominal pain and its frequency, bloating, altered stool frequency, and altered stool consistency. Improvement in the above-mentioned symptoms was attributed to pharmacological properties of ingredients of Jawarish Shahi i.e. Kasir-eriyah (carminative), Muqawwi meda (stomachic) wa Muqawwi A'ma (intestinal tonic) Muhallil (resolvent), Musakkin-e-alam

(analgesic), Qabiz (astringent) helps to reduce the intestinal motility, frequency of stool and regulate bowel movement.

To the best of our knowledge, this study is the first clinical trial that assessed the effects of JS for the treatment of symptomatic IBS adult patients, however, there are certain clinical studies in which of herbal medicinal products were used for IBS. Carmint a herbal drop that includes one herbal ingredient of JS (*Coriandrum sativum*) was studied in patients with active symptoms of IBS for 8-week. Carmint was found effective in reducing the severity of pain and bloating and was safe for patients with IBS which support the findings of our study.⁴⁶ The beneficial effects in our study may be attributed to different biomedical activities like antioxidant, immunomodulatory, gastro-protective, antispasmodic analgesic, antidiarrheal, antisecretory, anti-colitis, laxative cytoprotective, anti-inflammatory, anxiolytic, antidepressant present in phytochemicals of ingredients of JS. The beneficial effects on overall symptoms of IBS including severity, frequency and consistency of stool as well as the quality of life may be attributed to the “multiple herbs, multiple target” pharmacologic effects phenomenon, also characteristics of Unani Medicine like other traditional medicines and can be a potential treatment option and a drug for an explanation about the effects of JS on IBS. However, these results are too preliminary to reach the therapeutic application.

Since there was no control group, the improvement of IBS symptoms might not only be due to the treatment effect but also to placebo effect, we have chosen open-label and without control because we had to use the test drug in traditional dosage form and it was difficult for us to make a placebo. Another shortcoming is the small sample size, that is because of the covid-19 pandemic and the low turnout of the outpatient in the hospital, however, we have calculated the sample size on the base of a previous study. Although robust conclusions cannot be drawn at present from this study about the efficacy of JS on IBS, amelioration of IBS symptoms was evident. At the same time, quality of life significantly improved and JS was well tolerated without any adverse effect. One of the main rationales for choosing treatment options for any health condition and population, is if the intervention does no harm and has potential for benefit. Our encouraging results can be used to determine the power of future double blind, placebo-controlled trials which are needed to confirm these results.

5. Conclusion

Our trial revealed that the tested herbal formula JS was tolerable and effective in improving gut health and GI symptoms in adults with IBS disorders. The result of 45 days of treatment represents that JS confer therapeutic effects on IBS and its subtypes by improving gut health and reducing the severity and frequency of abdominal pain, distension, regulating stool frequency and consistency and finally improving quality of life. JS as a herbal preparation had several components and pharmacological effects, which may be as effective as conventional medications but with fewer side effects. Therefore, JS would be an alternative lead for the treatment of IBS.

Disclaimer

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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